Appl. No. 09/453,234
Amdt. dated [insert date]
Amendment under 37 CFR 1.116 Expedited Procedure
Examining Group

PATENT

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1.   (currently amended) A method of producing a human antibody display library, comprising:

providing a transgenic mouse whose genome comprises a plurality of human immunoglobulin genes that can be expressed to produce a plurality of human antibodies, wherein the transgenic mouse comprises less than the full complement of human immunoglobulin genes present in a human being;

isolating a population of nucleic acids encoding human antibody chains from lymphatic cells of the transgenic mouse by amplifying the population of nucleic acids using a set of primers selected based on which human immunoglobulin genes from the full complement of human immunoglobulin genes are present in the genome of the transgenic mouse;

forming a library of display packages displaying the antibody chains, wherein a library member comprises a nucleic acid encoding an antibody chain, and the antibody chain is displayed from the package, wherein the library comprises at least 100 members at least 50% of which comprise nucleic acids encoding human antibody chains showing at least 10^9 M^{-1} affinity for the same target and no library member constitutes more than 50% of the library.

2.   (original) The method of claim 1, further comprising producing RNA transcripts of the nucleic acids, and translating the transcripts to form antibody chains under conditions in which an antibody chain remains linked to the RNA transcript from which the antibody chain was translated, the complex formed between the transcript and the antibody chain constituting a library member.

3.   (original) The method of claim 1, further comprising cloning the population of nucleic acids into multiple copies of a phage display vector and expressing the vector in host cells to form the library of display packages.

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4. (previously presented) The method of claim 1, wherein the display package comprises a phagemid vector.

5. (previously presented) The method of claim 1, wherein the nucleic acids encode variable regions of the antibody chains and the display package comprises a segment encoding a human constant region and the cloning joins a nucleic acid encoding a variable region in-frame with the segment encoding the human constant region.

6. (original) The method of claim 5, wherein the antibody chain is a heavy chain and the constant region comprises a C_H1 region.

7. (original) The method of claim 5, wherein the antibody chain is a light chain and the constant region comprises a C_κ or C_λ constant region.

8. (original) The method of claim 1, wherein the antibody chain comprises a heavy or light chain which in at least some library members is complexed to a binding partner, comprising respectively a partner light or heavy human chain to form a Fab fragment.

9. (previously presented) The method of claim 1, further comprising contacting libraries members with a target, whereby library members displaying an antibody chain and binding partner (if present) with specific affinity for the target bind to the target, and separating display packages displaying antibody chains bound to the target to produce a subpopulation of display packages.

10. (previously presented) The method of claim 9, further comprising immunizing the transgenic mouse with an antigen.

11. (original) The method of claim 10, wherein the antigen is the target or an immunogenic fragment thereof.

12.   (original) The method of claim 1, wherein a library member further comprises a nucleic acid segment encoding a tag linked to the nucleic acid encoding the antibody chain, wherein the tag is the same in different library members.

13.   (original) The method of claim 12, further comprising contacting library members with a receptor having specific affinity for the tag and isolating a subpopulation of library members that bind to immobilized receptor.

14.   (original) The method of claim 13, further comprising contacting the subpopulation of library members with a target lacking specific affinity for the tag, and isolating a further subpopulation of library members that binds to the target.

15.   (previously presented) The method of claim 14, further comprising subcloning en masse nucleic acids encoding antibody chains from the further subpopulation of library members into multiple copies of an expression vector to form modified expression vectors.

16.   (original) The method of claim 15, further comprising expressing the modified expression vectors in host cells to produce a library of human antibody chains.

17.   (currently amended) A method of producing a human Fab phage display library, comprising:

providing a transgenic mouse whose genome comprises a plurality of human immunoglobulin genes that can be expressed to produce a plurality of human antibodies, wherein the transgenic mouse comprises less than the full complement of human immunoglobulin genes present in a human being;

isolating populations of nucleic acids respectively encoding human antibody heavy chains and human antibody light chains from lymphatic cells of the transgenic mouse by amplifying the populations of nucleic acids using a set of primers selected based on which

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human immunoglobulin genes from the full complement of human immunoglobulin genes are present in the genome of the transgenic mouse;

cloning the populations into multiple copies of a phage display vector to produce a display library, wherein a library member comprises a phage capable of displaying from its outersurface a fusion protein comprising a phage coat protein, a human antibody light chain or human antibody heavy chain, wherein in at least some members, the human antibody heavy or light chain is complexed with a partner human antibody heavy or light chain, the complex forming a Fab fragment to be screened, wherein the library comprises at least 100 members at least 50% of which comprise nucleic acids encoding Fab fragments showing at least $10^9 \, M^{-1}$ affinity for the same target and no library member constitutes more than 50% of the library.

18. (original) The method of claim 17, wherein the plurality of human genes is free of human lambda light chain genes.

19. (original) The method of claim 17, wherein there are no more than 40 human VH genes included in the plurality of human genes.

20. (original) The method of claim 17, wherein there are no more than 40 human VL genes included in the plurality of human genes.

21. (original) The method of claim 17, wherein each copy of the phage display vector receives a random combination of nucleic acids encoding heavy and light chains from the respective populations.

22. (original) The method of claim 17, wherein the populations of nucleic acids respectively encode populations of human heavy and light chain variable regions, and the phage display vector encodes human heavy and light chain constant regions expressed in frame with human heavy and light chains inserted into the vector.

23.　(previously presented)　The method of claim 17, further comprising contacting libraries members from the display library with a target, whereby library members displaying a Fab fragment with specific affinity for the target bind to the target, and separating phage displaying Fab fragments bound to the target to produce a further subpopulation of phage.

24.　(original)　The method of claim 23, further comprising isolating a phage displaying a Fab fragment that binds to the target.

25.　(previously presented)　The method of claim 17, further comprising immunizing the transgenic mouse with an antigen.

26.　(original)　The method of claim 24, further comprising expressing a Fab fragment from a phage bound to the target in soluble form.

27.　(original)　The method of claim 17, wherein the fusion protein further comprises a tag that is the same in different library members.

28.　(original)　The method of claim 27, further comprising contacting library members with a receptor that specifically binds to the tag, and isolating a subpopulation of library members bound to the receptor.

29.　(original)　The method of claim 28, further comprising contacting the subpopulation of library members with a target lacking specific affinity for the tag, and isolating a further subpopulation of library members bound to the target.

30.　(original)　The method of claim 29, further comprising subcloning a mixed population of nucleic acids encoding human antibody heavy chains and human antibody light chains from the further subpopulation of library members into multiple copies of an expression vector to produce modified expression vectors.

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31.　　(original)　The method of claim 30, further comprising expressing the modified expression vectors in host cells to produce a population of human antibodies.

32.　　(original)　The method of claim 31, wherein the population of human antibodies includes at least 10 different antibodies.

33.　　(original)　The method of claim 32, wherein the population of human antibodies includes at least 100 different antibodies.

34.　　(original)　The method of claim 33, wherein the population of human antibodies includes at least 1000 different antibodies.

35-46.　Canceled